CURRENT ONCOLOGY COMMENTARY

Has screening mammography become obsolete?

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With so much debate about the value of screening mammography and with the emergence of newer technologies, it seems reasonable to ask whether screening mammography, as we know it, has become obsolete. Some believe that mammography is associated with so many harms that retrenchment from the years of screening advocacy is the only sensible path. Since 2009, guidelines from the U.S. Preventive Services Task Force (USPSTF)[1] have emphasized the negative balance of annual screening and screening before age 50 and after age 74. Others believe that the positive aspects of screening—a 20%–30% reduction in breast cancer mortality reported by European trials dating to the early 1990s—demonstrate that benefits outweigh harms. The latest review of screening pros and cons by the International Agency for Research on Cancer[2] is worth noting. The USPSTF update is due soon, but drafts of the proposed update suggest no major changes from the 2009 guideline[3].

The quality of randomized studies using a "no screening" control has been debated for more than 20 years. There are really no new discussions that will change anyone's mind. New trials are unlikely because of the ethical impossibility of having a control group that is denied a proven screening technology (mammography), the length of time required to follow participants, and the costs of large studies. But several areas of controversy seem to me to be useful to reconsider: namely, the balance of benefits to harms, and more importantly, the benefits or harms included in any given study.

THE "HARMS" OF SCREENING MAMMOGRAPHY

The generally cited harms of screening[1] are these:

- Overdiagnosis
- Overtreatment
- False-positive tests
- Unnecessary biopsies
- Psychological and physical distress
- Unnecessary costs

Overdiagnosis

Critics usually define "overdiagnosis" to include both invasive and noninvasive (ductal carcinoma *in situ*, lobular carcinoma *in situ*) breast cancers. A number of reports have rightly observed that *in situ* cancers should not be considered in the same way as invasive cancers. Indeed, perhaps they should not be considered cancers at all[4]. All would agree that many *in situ* cancers never become clinically important or troublesome. The difficulty rests in our imperfect ability to sort the lesions that have a short-term invasive future from those that do not. A U.S. National Cancer Institute working group has recommended dropping the term "carcinoma" from the names of *in situ* disease because that term can trigger treatment when no treatment would be appropriate. The group has urged that *in situ* diseases be called IDLES (indolent lesions of epithelial origin). However, a recent report from Narod *et al.*[5] based on 108,196 registry cases of ductal carcinoma *in situ* might well modify that view. Narod reported that age greater than 35 years, black race, a large tumour, a high-grade tumour, or a tumour with comedonecrosis are all associated with a significantly greater risk of breast cancer death. The implications for treatment adjustments were discussed in an accompanying editorial by Esserman and Yau[6].

The claim that invasive breast cancers are overdiagnosed is another matter. Fewer than 10% of invasive cancers have been histopathologically classified as less-aggressive types (for example, medullary or tubular carcinomas). Even so, such cancers are often associated with local spread that requires local attention. But the remaining 90% of breast carcinomas have the real possibility of a lethal outcome for the host. It could be that, in time, molecular profiling will be able to clearly distinguish disease that can be treated safely but minimally. I submit that, for the time being, judgment be withheld on whether any of the remaining 90% of invasive cancers should be considered clinically not important.

Overtreatment

"Overtreatment" of noninvasive carcinomas is a matter of contention. Although a ductal carcinoma *in situ* that is extensive, with a high nuclear grade and small margins, in a younger woman would be treated by most oncologists as serious and posing a fairly immediate invasive threat, less-aggressive forms of *in situ* disease are considered by many to be reasonably viewed as compatible with a wait-and-see attitude.

Except for the 10% of less-aggressive invasive carcinomas, "overtreatment of invasive cancers" is a matter of judgment among oncologists. Some prefer to treat too much to avoid treating too little. But almost all oncologists are committed to the study of new, potentially more effective, less toxic, and less extensive treatments that can result in prevention of recurrence or death.

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"Overtreatment" is *not* the fault of mammography, but of the interpretation of "appropriate therapy" as dictated by the pathology findings. Much progress has been made in sorting invasive cancers by their molecular profiles and aggressive potential, but oncologists are still unsure about how much treatment is appropriate and what the most effective treatment is. The plethora of adjuvant trials speaks to those insecurities.

Unnecessary Follow-up Mammograms, False-Positive Tests, and Unnecessary Biopsies

As the USPSTF points out, the unwanted aspects of screening mammography are the number of times radiologists call a finding "suspicious" and ask for a recall or recommend biopsy, only to discover no serious abnormality. However, that is the price always paid with a complex screening test. The more sensitive the test (finding cancers), the less specific it is (finding non-cancers). Claims about the harms of mammography rest on the high number of false-positive tests and biopsies. A 2006 audit[7] reported results of the widespread use of the BI-RADS (Breast Imaging—Reporting and Data System) categories and contemporary standardized training of radiologists. Of 2,580,151 screening mammograms obtained between 1998 and 2003, fewer than 10% were recalls. Of the recalls, 10% resulted in biopsies. Of the biopsies, 66% were benign, and 26% showed invasive carcinomas. The median size of invasive lesions was 1.3 cm, with 37% being smaller than 1 cm and only 21% being larger than 2 cm[8]. Because the purpose of mammography is to find lesions that are small and nonpalpable, the trade-off with false positives seems to me to be worthwhile.

Psychological and Physical Distress

Historically, much has been made about the psychological and physical distress caused by unnecessary mammograms, recalls, biopsies, and treatments. When the public health campaign for screening mammography began in the early 1980s, not many women understood the process. The equipment was older; many private machines did not produce clear images; compression took longer; and technicians were often unsympathetic. Beginning in the 1990s, great improvements were made. Mammography machines are now standardized by physicists and provide sharp images. Compression lasts only a few seconds. Technicians undergo special training and radiologists are trained to recognize and report the BI-RADS categories. Initial biopsies are usually performed under local anesthesia in the radiology suite with a thin needle. No surgery is required, complications are few, and such procedures have become a "non-event" as more and more women understand the process and its rationale. The result is that physical and psychological distress is at a minimum. Weighed against the possible gain from finding an early, easily treatable invasive cancer, the negative psychological and physical aspects of undergoing mammography and biopsy seem negligible.

Unnecessary Costs

The costs of performing annual mammograms, including in women 40–49 years of age, and of paying for treatments that are not necessary are legitimate concerns that have to be addressed. There is no argument that the incidence of invasive breast cancer is less in women under 50 years of age, although the disease is no less lethal and is more often lethal than it is in older women. Given small differences in incidence between the 40–49 age group and the 50–69 age group, and the longer expected normal life span of a 44-year-old compared with a 74-year-old, it is hard to understand why there is not a compelling reason to screen the younger women. One answer is that few firm supportive data have emerged from the randomized trials of the 1980s and 1990s. But remember that mammography then is not at all comparable with the discriminatory powers of modern technology, particularly in women whose breasts often are dense and unrevealing to poorer imaging powers.

Adhering to the USPSTF recommendation of biannual mammograms in women 50–74 years of age would certainly save costs. A modelling study[8] reported that increasing the interval from the recommended annual interval would result in "only" a 19% increase in mortality. I leave it to the reader to wrestle with the issue of whether such an increase is or is not meaningful!

DOES MODERN THERAPY REPLACE THE NEED FOR MAMMOGRAPHY?

Mammography critics actively promote the idea that because modern therapy is saving lives, mammography is less useful. But in spite of modern therapies, women with larger cancers or positive lymph nodes *usually* do not survive as long or enjoy as long a disease-free survival as those with node-negative smaller disease. The data supporting chemotherapy "cures" of breast cancer are slim, but seem to come from trials in which smaller tumour sizes are reported (T1a: >1 mm to ≤5 mm; T1b: >5 mm to ≤10 mm; T1c: >10 mm to ≤20 mm). In adjuvant trials, invasive cancers smaller than 1 cm appear to have straight-line survival curves at 90% or more; larger cancers seem to follow a downward slope, with some slopes being less steep than others depending on the cancer's characteristics and the therapies administered.

With modern technology, the median size of cancers found by mammography in someone undergoing *regular* screening is 1 cm or smaller and can be as small as 0.5 cm. If the median doubling time of breast cancer cells is 180 days, then moving the mammography interval from 1 year to 2 years allows 1 or 2 doublings to occur and size to change to more than 0.5–1 cm from 0.5 cm. Such a seemingly small change in size is associated with a doubling (or more) of the mortality rate, regardless of whether the nodes are negative or positive. Classical literature supports the view that, as size increases, so usually does the chance of positive lymph nodes, which in turn are usually associated with decreased survival (Table I).

A WORD OF CAUTION ABOUT THE ROLE OF SIZE AND LYMPH NODE STATUS

Based on the teachings of classical oncology, subscription to these two general principles is common:

- Bigger cancers require more complex therapy than smaller ones.

- With time, invasive cancers grow, mutations increase, lymph node positivity appears, systemic dissemination becomes more likely, the body's burden of disease increases, and treatment is less successful.

There are of course important exceptions to those generalities. The most obvious are the small, very aggressive cancers that represent malignancies that do not require time to grow and mutate but that have aggressive potential from the get-go. Are size or lymph node status then not important?

The situation is complicated. Modern biology and pathology have moved beyond the histopathology of breast cancers into the realm of subtypes based on molecular biology and multigene expression. Size and lymph node status still matter, but in a restricted sense. Some small cancers have unfortunate molecular and pathologic signatures (triple negative, undifferentiated, highly mitotic). Untreated, they are highly malignant. Improvements in the ability to identify some of the molecular biology of breast cancer lesions have made an enormous impact on the resulting recommendations for treatment. The use of standard markers (estrogen receptor, progesterone receptor, HER2) and the addition of newer ones have all been useful in estimating the risk of recurrence and identifying appropriate treatment. Ongoing work in identifying molecular "fingerprints" for individual cancers is resulting in updated classifications of breast cancer subtypes that suggest new specific immunologic treatments and targeted therapies. *The reader should note that, in a small number of cases, the relationships between tumour size, nodal status, and survival could be more complex, less linear, and less direct than had previously been supposed.*

THE HARMS OF *NOT* SCREENING

The harms or costs of *not* screening—apart from an increase in breast cancer mortality and a decrease in lifespan—are these:

- Treatable or curable cancers being missed
- Fewer smaller cancers being found
- More larger cancers being found, with larger cancers *usually* being associated with
  - more positive lymph nodes;
  - more surgery;
  - more radiation therapy;
  - more chemotherapy, hormonal therapy, and immunotherapy;

  which all entail
  - more financial costs for the appropriate treatments;
  - more follow-up screening and medical care after initial therapy;
  - more psychological distress, often lasting a lifetime;
  - more physical distress because of the larger or more advanced cancer; and
  - more socioeconomic and family problems.

How can the list of harms of *not* screening possibly be balanced with the harms of screening? Only a small body of evidence is available from randomized studies of the total costs of treating women whose cancers were not diagnosed when very small. Most such trials focus only on the financial costs of the drugs or on the side effects of therapy[10]. More information comes from descriptive studies, which usually highlight a few salient problems[11].

TABLE I 5-Year breast cancer mortality rate in relation to tumour size and lymph node status[a]

Size (cm)	Mortality rate (%) by lymph node status		
	Negative	1-3 Positive	>3 Positive
<0.5	0.8	4.7	41.0
0.5–0.09	1.7	6.0	45.8
1–1.9	4.2	13.4	32.8
2–2.9	7.7	16.6	36.6

[a] Derived from the table in Carter *et al.*[9], which was in turn derived from U.S. Surveillance, Epidemiology, and End Results data.

Is it possible to calculate *all* the "costs"? Of the treatment itself? Of its side effects? Of pain, suffering, and death? Of the rigours of life-long therapy, loss of income, family disruption or personal bankruptcy? Compared with those problems, a false-positive mammogram or the pain of a fine-needle biopsy seems trivial. Do the harms of *not* screening outweigh the harm of screening? How much "cost" is there in missing small, node-negative invasive breast cancers, and how much cost is there in treating large or recurrent disease? I believe that the negative aspects of our complex therapies completely swamp the negative aspects of mammography.

Much more data will have to be generated. Hopefully, future assessments will include not only statisticians and epidemiologists, but also practicing oncologists, patients, and families so that the true costs of *not* screening can be identified. Whatever the outcome of such data generation and analysis, it is intellectually dishonest not to try to measure the negative results of *not* screening just because they are "difficult to measure" or because no one has yet bothered to study them.

CONFLICT OF INTEREST DISCLOSURES

I have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and I declare that I have none.

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